

<https://helda.helsinki.fi>

The Incidence of Trilateral Retinoblastoma : A Systematic Review and Meta-Analysis

De Jong, Marcus C.

2015-12

De Jong , M C , Kors , W A , De Graaf , P , Castelijns , J A , Moll , A C & Kivela , T 2015 , ' The Incidence of Trilateral Retinoblastoma : A Systematic Review and Meta-Analysis ' , American Journal of Ophthalmology , vol. 160 , no. 6 , pp. 1116-1126 . <https://doi.org/10.1016/j.ajo.2015.09.009>

<http://hdl.handle.net/10138/223832>

<https://doi.org/10.1016/j.ajo.2015.09.009>

publishedVersion

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.

This reprint may differ from the original in pagination and typographic detail.

Please cite the original version.

The Incidence of Trilateral Retinoblastoma: A Systematic Review and Meta-Analysis



MARCUS C. DE JONG, WIJNANDA A. KORS, PIM DE GRAAF, JONAS A. CASTELIJNS, ANNETTE C. MOLL, AND TERO KIVELÄ

- **PURPOSE:** To estimate the incidence of trilateral retinoblastoma in patients with retinoblastoma.
- **DESIGN:** Systematic review and meta-analysis.
- **METHODS:** We searched Medline and Embase for scientific literature published between January 1966 and July 2015 that assessed trilateral retinoblastoma incidence. We used a random-effects model for the statistical analyses.
- **RESULTS:** We included 23 retinoblastoma cohorts from 26 studies. For patients with bilateral retinoblastoma the unadjusted chance of developing trilateral retinoblastoma across all cohorts was 5.3% (95% confidence interval [CI]: 3.3%–7.7%); the chance of pineal trilateral retinoblastoma was 4.2% (95% CI: 2.6%–6.2%) and the chance of nonpineal trilateral retinoblastoma was 0.8% (95% CI: 0.4%–1.3%). In patients with hereditary retinoblastoma (all bilateral cases, and the unilateral cases with a family history or germline *RB1* mutation) we found a trilateral retinoblastoma incidence of 4.1% (95% CI: 1.9%–7.1%) and a pineal trilateral retinoblastoma incidence of 3.7% (95% CI: 1.8%–6.2%). To reduce the risk of overestimation bias we restricted analysis to retinoblastoma cohorts with a minimum size of 100 patients, resulting in adjusted incidences of 3.8% (95% CI: 2.4%–5.4%), 2.9% (95% CI: 1.9%–4.2%), and 0.7% (95% CI: 0.3%–1.2%) for any, pineal, and nonpineal trilateral retinoblastoma, respectively, among patients with bilateral retinoblastoma. Among hereditary retinoblastoma we found an adjusted trilateral retinoblastoma incidence of 3.5% (95% CI: 1.2%–6.7%) and a pineal trilateral retinoblastoma incidence of 3.2% (95% CI: 1.4%–5.6%).
- **CONCLUSION:** The estimated incidence of trilateral retinoblastoma is lower than what is reported in previous literature, especially after exclusion of small

cohorts that were subject to overestimation bias in this context. (*Am J Ophthalmol* 2015;160(6): 1116–1126. © 2015 by Elsevier Inc. All rights reserved.)

UNTIL THE AGE OF ABOUT 7 YEARS PATIENTS WITH hereditary retinoblastoma are at risk of having an intracranial midline primitive neuroectodermal tumor diagnosed, and among patients diagnosed since 1995 more than 95% have developed trilateral retinoblastoma before the age of 5 years.^{1–3} In histopathologic analysis these tumors look similar to corresponding retinal tumors. When unilateral or bilateral retinoblastoma and an intracranial midline primitive neuroectodermal tumor both occur in a patient, this is referred to as trilateral retinoblastoma, which can be found in the pineal gland (pineal trilateral retinoblastoma) in about three-quarters of cases; in the remaining patients it develops in other midline brain regions (nonpineal trilateral retinoblastoma), usually the suprasellar and parasellar region, although other brain regions have been reported also.^{3–5}

In a recent meta-analysis we showed that survival has improved considerably in the last 2 decades, from hardly any to almost half of all patients.³ Favorable survival after pineal trilateral retinoblastoma depended strongly on early detection and small tumor size. The improved survival after trilateral retinoblastoma was highly associated with the use of (improved) chemotherapy regimens, especially high-dose chemotherapy with stem cell rescue.³

Previous radiotherapy for retinoblastoma, especially before the age of 12 months, has been associated with a potentially higher incidence of pineal trilateral retinoblastoma in patients with hereditary retinoblastoma, even though the pineal gland is usually not (directly) within the field of radiation.⁶ Whether previous systemic chemotherapy is protective of developing trilateral retinoblastoma is still being debated.^{7–10}

There have been numerous reports on trilateral retinoblastoma incidence, but these studies are quite heterogeneous. Some are referral-based, others population-based. The only previously published study summarizing incidence data across studies reported an incidence of 5%–15% among patients with bilateral retinoblastoma.²

The objective of this study is to provide an overview of, to critically analyze, and to provide pooled summary estimates of published incidence data for pineal and nonpineal trilateral retinoblastoma.



Supplemental Material available at AJO.com.

Accepted for publication Sep 7, 2015.

From the Departments of Radiology and Nuclear Medicine (M.C.d.J., P.d.G., J.A.C.), Pediatric Oncology (W.A.K.), and Ophthalmology (A.C.M.), VU University Medical Center, Amsterdam, Netherlands; and Department of Ophthalmology (T.K.), University of Helsinki and Helsinki University Hospital, Helsinki, Finland.

Inquiries to Marcus C. de Jong, Department of Radiology and Nuclear Medicine, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, the Netherlands; e-mail: mc.dejong@vumc.nl

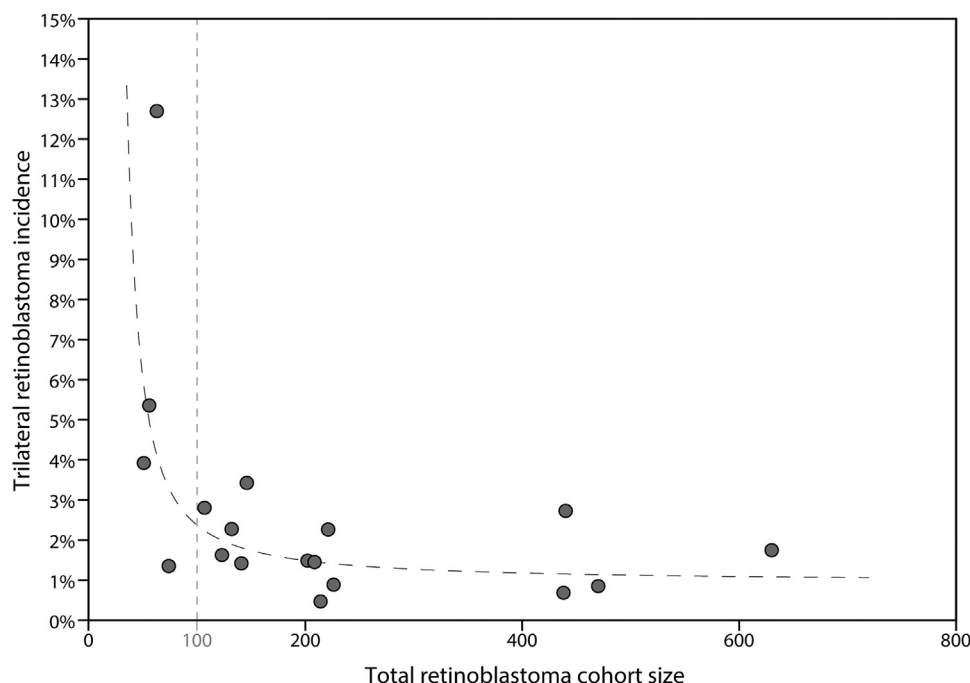


FIGURE 1. Trilateral retinoblastoma incidence vs the size of the cohorts of patients with unilateral or bilateral retinoblastoma. The estimated curve in this figure is an S-curve with a fit of $R^2 = 0.44$, $P = .0027$.

METHODS

WE PERFORMED THIS SYSTEMATIC REVIEW AND META-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.^{11,12}

• **SEARCH STRATEGY:** We searched Medline (PubMed) and Embase for English, Dutch, and German literature published from January 1, 1966 through July 15, 2015, evaluating trilateral retinoblastoma cases. We also considered alternatively found studies for inclusion (eg, through checking references in included studies). The search was similar to the search we used in our systematic review and meta-analysis on survival of patients with trilateral retinoblastoma.³ To ensure a sensitive search, we included only keywords corresponding to the target condition (including retinoblastoma, pineoblastoma, pineal, suprasellar, parasellar, sellar, ectopic, and brain), without any delimiters. For the detailed search see [Supplemental Table 1](#) (available at [AJO.com](#)).

• **STUDY SELECTION AND DATA EXTRACTION:** Two authors (M.C.J. and A.C.M.) independently reviewed article titles and abstracts for eligibility. Discrepancies were resolved by consensus. Subsequently the same 2 authors independently reviewed eligible full-text articles for inclusion in the systematic review and meta-analysis. Again, discrepancies were solved by consensus.

We included studies in the systematic review and meta-analysis if (1) the study mentioned the number of patients with trilateral retinoblastoma (can also be 0, as long as authors mentioned evaluating for trilateral retinoblastoma cases), if (2) articles reported details and size of the retinoblastoma cohort in which patients with trilateral retinoblastoma were seen (eg, number of patients with trilateral retinoblastoma diagnosed in a cohort of patients with retinoblastoma during a certain period), and if (3) the full-text article could be obtained. We excluded studies from the systematic review if (1) the article was a review or meta-analysis, and if (2) studies included overlapping incidence data. Two authors (M.C.J. and W.A.K.) independently extracted incidence data. Discrepancies were resolved by consensus. We have defined hereditary retinoblastoma as patients with bilateral retinoblastoma, known familial retinoblastoma, or a detected germline mutation in *RB1*.

• **DATA SYNTHESIS AND STATISTICAL ANALYSIS:** Ideally, we would present the cumulative incidence of trilateral retinoblastoma until a certain age (eg, up to 5 years) in comparable retinoblastoma cohorts; however, most studies only provided the total number of patients with retinoblastoma and the number of trilateral retinoblastoma cases they found in their cohort. Therefore we are restricted to the calculation of a percentage of cases that developed trilateral retinoblastoma divided by total retinoblastoma cohort from a certain time period. This method unfortunately does

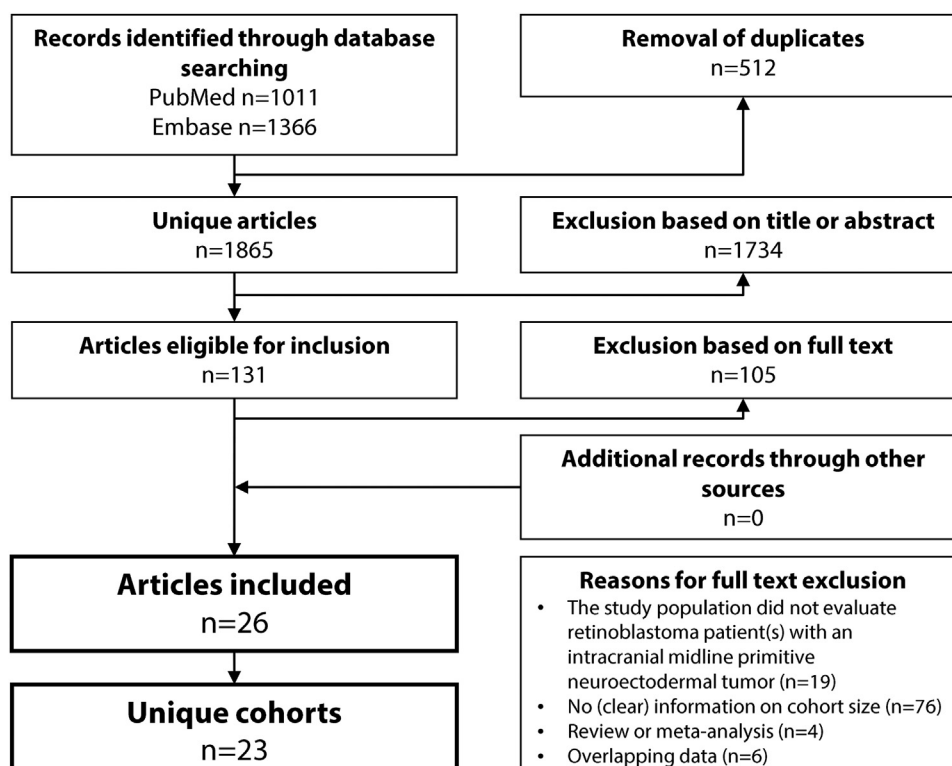


FIGURE 2. Flow chart of the total number of articles found with PubMed and Embase and subsequent inclusion and exclusion of articles, leading to the number of included articles and retinoblastoma cohorts that contained information on trilateral retinoblastoma incidence.

not take into account the effect of patients lost to follow-up (ie, assuming that of all patients with retinoblastoma it is unequivocally known whether they developed trilateral retinoblastoma or not).

In addition to performing unadjusted analysis, we calculated adjusted estimates by including cohorts of at least 100 patients with retinoblastoma, to prevent overestimation bias. Most small cohorts published specifically after encountering at least 1 trilateral retinoblastoma and thus led to a report irrespective of how many patients without trilateral retinoblastoma had been seen (ie, an arbitrary cohort of patients with retinoblastoma with a certain start and end date will have been constructed around the patient(s) with trilateral retinoblastoma that were encountered). The limit of 100 patients was based on visual evaluation of a plot of the incidence of trilateral retinoblastoma against the total sample size across studies (Figure 1). Typically, an unselected patient population contains 40% of bilateral retinoblastoma, and thus we considered also a cohort of at least 40 bilateral retinoblastomas to be large enough to guard for overestimation bias.

To assess the extent of this bias we compared data from developed vs developing countries, as one would expect follow-up to be more complete in developed countries (ie, higher chance to find a trilateral retinoblastoma). This might lead to an underestimation of trilateral retino-

blastoma incidence in the developing countries. Pooling data from different retinoblastoma cohorts also assumes comparability of these cohorts.

To evaluate changes in trilateral retinoblastoma incidence over time we used a cutoff at the year 1995. We chose this cutoff because around (or maybe even before) 1995 treatment of retinoblastoma started to shift from radiotherapy to chemotherapy.¹³

We used a random-effects model to calculate summary estimates of trilateral retinoblastoma incidence.^{14,15} A random-effects model is used for meta-analyses to account for heterogeneity between studies. For each analysis we calculated I^2 to evaluate heterogeneity among included studies; I^2 ranges from 0 to 100% with increasing heterogeneity.¹⁶ For the random-effects analyses we used MetaXL (version 2.1; EpiGear, Wilston, Australia) and SAS (Proc MIXED, version 9.3; SAS, Cary, North Carolina, USA). The forest plots were created with Illustrator CS6 (Adobe, San Jose, California, USA).

• **RISK OF BIAS AND STUDY QUALITY ASSESSMENT:** Two authors (M.C.J. and T.K.) assessed the risk of bias with a modified checklist that was developed for prevalence studies by Hoy and associates.¹⁷ With the checklist 6 items that could lead to bias were assessed (Supplemental Table 2, available at AJO.com).^{18,19}

TABLE 1. Basic Information About the Retinoblastoma Cohorts of All Included Studies That Presented Trilateral Retinoblastoma Incidence Data

Study	Inclusion Period	Country	Source of the Data	Type of Patients With Retinoblastoma	Age at Retinoblastoma Diagnosis (Months)	Patient Follow-up From Retinoblastoma Diagnosis (Months)	Percentage of Cohort With Unilateral Retinoblastoma	Percentage of Cohort With Bilateral Retinoblastoma	Percentage of Cohort With Familial Retinoblastoma	Study Cohort (Partly) Overlaps With
Amoaku et al ²⁶	1960–1994	United Kingdom	Population registry	Any	Mean 6, range 0.75–17		64%	36%	38 ^a	
Antoneli et al ²⁷	1986–2003	Brasil	1 center	Any			60%	40%		
Azar et al ²⁸	1975–2001	Australia	2 centers	Any	Mean 17.9 (bilateral 22.6, unilateral 3.5)		60%	40%	11	
Bartuma et al ²⁹	2001–2011	Sweden	1 center	Hereditary	Mean 8, range 0–39	Mean 60, range 13–144	8%	92%	38	
Blach et al ²²	1979–1990	USA	1 center	Irradiated	Median 7, range <1–60	Median 68, range 4–153	17%	83%	27	
Chantada et al ¹⁰	1988–2012	Argentina	1 center	Bilateral	Mean 13.9, range 0–114	Median 115, range 31–290		100%	14 ^a	Moreno et al ³⁰
De Ioris et al ³¹	1999–2009	Italy	1 center	Any	Median 10, range 0.5–73		58%	42%	14	
De Potter et al ³²	1972–1992	United Kingdom	1 center	Any			54%	46%	14	
Duncan et al ³³	1990–1998	USA	2 centers	Any		Mean 44.8, range 0–139	≥63%	≤37%		
Helveston et al ³⁴	1967–1987	USA	1 center	Any	Unilateral 23, bilateral 10 ^b		59%	41%		
Imhof et al ²³	1971–1993	Netherlands	1 center	Irradiated	Mean 5, range 1–216	Mean 148, range 48–276				Moll et al ⁶
Jubran et al ³⁵	1991–1999	USA	1 center	Any						
Jurkiewicz et al ³⁶	1996–2008	Poland	1 center	Any	Unilateral median 22, bilateral median 12					
Kingston et al ³⁷	1954–1983	United Kingdom	2 centers	Any			31%	69%		
Klufas et al ²⁴	2006–2010	USA	1 center	Treated with intraarterial chemotherapy		Median 17.5, range 8–36				
Lim et al ³⁸	2001–2009	Malaysia	1 center	Any						
Lim et al ³⁹	1997–2010	Singapore	1 center	Any	25.7, SD 19.9 (unilateral mean: 30.2, SD 21.4, bilateral mean: 15.4, SD 9.6)	Median 36, range 0–156	69%	31%		

Continued on next page

TABLE 1. Basic Information About the Retinoblastoma Cohorts of All Included Studies That Presented Trilateral Retinoblastoma Incidence Data (Continued)

Study	Inclusion Period	Country	Source of the Data	Type of Patients With Retinoblastoma	Age at Retinoblastoma Diagnosis (Months)	Patient Follow-up From Retinoblastoma Diagnosis (Months)	Percentage of Cohort With Unilateral Retinoblastoma	Percentage of Cohort With Bilateral Retinoblastoma	Percentage of Cohort With Familial Retinoblastoma	Study Cohort (Partly) Overlaps With
Lueder et al ⁴⁰	1924–1985	USA	1 center	Any			67%	33%	14	Lueder et al ⁴¹
Lueder et al. ⁴¹	1924–1989	USA	1 center	Any					14	Lueder et al ⁴⁰
Moll et al ⁶	1970–1997	Netherlands	Population registry	Hereditary						Imhof et al ²³
Moreno et al ³⁰	2000–2009	Argentina	Population registry	Any	Unilateral median 26 (IQR 13–42), bilateral median 10 (IQR 5–19)		68%	32%		Chantada et al ¹⁰
Popovic et al ²⁵	1990–2001	Switzerland	1 center	Any			49%	51%		
Provenzale et al ⁴²	1985–2002	USA	1 center	Any			52%	48%		
Ramasubramanian et al ^{8,21}	2000–2012	USA	1 center	Any	Mean 21, median 13, range 0–91		53%	47%	11	
Scott et al ⁴³	1970–1990	USA	1 center	Any	Mean 15.8 (nonhereditary mean 20.5, hereditary mean 11.7)		52%	48%		
Shields et al ²⁰	1995–1999	USA	1 center	Any	Mean 14, median 8, range 1–87	Mean 33, range 0–67	48%	52%	18	

IQR = interquartile range; SD = standard deviation.

^aAs percentage of the patients with bilateral retinoblastoma.

^bAge at treatment; unknown if these are means or medians or some other measure.

RESULTS

WE IDENTIFIED 1865 UNIQUE STUDIES FROM DATABASE searches. We excluded 1734 articles based on title and abstract (Figure 2). We excluded 105 studies based on the full text; reasons for exclusion are shown in Figure 2. Twenty-six studies (3 pairs of studies had overlapping cohorts but provided different data of interest and were therefore included; see Table 1) met the inclusion criteria of this systematic review. Twenty-one studies (20 cohorts) were included in the meta-analysis. Tables 2 and 3 show the incidence data as reported in each included study.

- **UNADJUSTED ESTIMATES:** Twenty-six studies reported trilateral retinoblastoma incidence in 23 unique cohorts of patients with retinoblastoma, and in 15 studies (15 cohorts) bilateral could be distinguished from unilateral retinoblastoma (Table 2). Seven studies (6 cohorts) presented the trilateral retinoblastoma incidence in hereditary retinoblastoma, 3 studies (cohorts) reported trilateral retinoblastoma incidence after external beam irradiation for retinoblastoma, and 5 studies (cohorts) compared the incidence in patients with retinoblastoma with and without previous chemotherapy. Forest plots of the included studies (sorted by the midpoint of the study period) and the summary estimates are shown in Figure 3.

For unilateral and bilateral retinoblastoma combined, the unadjusted chance of developing a trilateral retinoblastoma across all studies is 2.1% (95% confidence interval [CI]: 1.4%–2.8%; 18 cohorts), the chance of developing pineal trilateral retinoblastoma is 1.7% (95% CI: 1.2%–2.3%; 19 cohorts), and the chance of a nonpineal trilateral retinoblastoma is 0.4% (95% CI: 0.2%–0.6%; 18 cohorts). For bilateral retinoblastoma the chance of developing a trilateral retinoblastoma is 5.3% (95% CI: 3.3%–7.7%; 14 cohorts); restricting calculations to pineal trilateral retinoblastoma resulted in an incidence of 4.2% (95% CI: 2.6%–6.2%; 15 cohorts) and restricting to nonpineal trilateral retinoblastoma gave an incidence of 0.8% (95% CI: 0.4%–1.3%; 14 cohorts). In hereditary retinoblastoma we found a trilateral retinoblastoma incidence of 4.2% (95% CI: 1.6%–7.7%; 5 cohorts) and a pineal trilateral retinoblastoma incidence of 3.7% (95% CI: 1.8%–6.2%; 6 cohorts), and we did not calculate the nonpineal trilateral retinoblastoma incidence, as there were no cases in 5 retinoblastoma cohorts.

- **ADJUSTED ESTIMATES:** We adjusted for potential overestimation bias by restricting the analysis to cohorts that included at least 100 patients with retinoblastoma (Figure 1). We found incidences of 1.7% (95% CI: 1.2%–2.2%; 14 cohorts), 1.4% (95% CI: 1.0%–1.7%; 15 cohorts), and 0.3% (95% CI: 0.2%–0.6%; 14 cohorts) for any, pineal, and nonpineal trilateral retinoblastoma, respectively. In cohorts with only patient with bilateral retinoblastoma

we found incidences of 3.8% (95% CI: 2.4%–5.4%; 10 cohorts), 2.9% (95% CI: 1.9%–4.2%; 11 cohorts) and 0.7% (95% CI: 0.3%–1.2%; 10 cohorts), respectively. Among patients with hereditary retinoblastoma we found a trilateral retinoblastoma incidence of 3.5% (95% CI: 1.2%–6.7%; 4 cohorts) and a pineal trilateral retinoblastoma incidence of 3.2% (95% CI: 1.4%–5.6%; 5 cohorts).

- **PERIOD ANALYSIS:** To analyze changes over time we created 2 groups with the year 1995 as the cutoff year (depending on the midpoint of the study period). Before the year 1995 unadjusted trilateral retinoblastoma incidence for unilateral and bilateral retinoblastoma combined was 2.5% (95% CI: 1.5%–3.8%) vs 1.5% (95% CI: 0.9%–2.2%) from the year 1995 onward ($P = .24$). The incidence of pineal trilateral retinoblastoma before the year 1995 was 2.2% (95% CI: 1.3%–3.4%) vs 1.2% (95% CI: 0.8%–1.8%) from 1995 onward ($P = .14$).

Restricted to patients with bilateral retinoblastoma, the unadjusted trilateral retinoblastoma incidence was 6.2% (95% CI: 3.2%–9.9%) before the year 1995 vs 3.7% (95% CI: 1.4%–6.9%) from the year 1995 onward ($P = .44$). The incidence of pineal trilateral retinoblastoma was 5.3% (95% CI: 2.7%–8.8%) before the year 1995 vs 2.9% (95% CI: 1.3%–5.1%) from the year 1995 onward ($P = .38$; Figure 3).

- **EFFECT OF PREVIOUS THERAPY:** Four studies reported on trilateral retinoblastoma incidence in retinoblastoma cohorts who underwent previous systemic chemotherapy (Table 3). In a single-center study with 4 trilateral retinoblastoma cases an inverse association between chemotherapy and the development of pineoblastoma was reported ($P = .014$), with an incidence of 0.6% (1/180) and 8.6% (3/35), respectively, for patients who did and who did not receive previous chemotherapy for their retinoblastoma.⁸ In a single-center study from the same center, but different period, 1 pineoblastoma was found in 18 hereditary patients with retinoblastoma who did not undergo chemotherapy, compared to none in 99 patients who did undergo chemotherapy.²⁰ However, in another single-center study with 3 trilateral retinoblastomas this association was reversed with an incidence of 1.9% (3/159) vs 0.0% (0/38), respectively ($P > .99$).¹⁰

Three studies specifically looked at trilateral retinoblastoma incidence in cohorts of patients with retinoblastoma who underwent external beam radiotherapy (Table 3). In a single-center study with 4 trilateral retinoblastomas a pineal trilateral retinoblastoma incidence of 1.7% (3/179) was found in the group of patients with nonirradiated hereditary retinoblastoma and an incidence of 2.8% (1/36) was found in the irradiated group ($P = .5$).^{8,21} A single-center study with 6 trilateral retinoblastomas found that patients with bilateral retinoblastoma who underwent irradiation as treatment for their retinoblastoma had a 6.2%

TABLE 2. Incidence of Trilateral Retinoblastoma Among Unilateral and Bilateral Retinoblastoma, Bilateral Retinoblastoma, and Hereditary Retinoblastoma for Studies Included in the Meta-analysis

Study	Inclusion Period	Unilateral and Bilateral Retinoblastoma		Bilateral Retinoblastoma		Hereditary Retinoblastoma	
		Pineal	Nonpineal	Pineal	Nonpineal	Pineal	Nonpineal
Amoaku et al ²⁶	1960–1994	2.7% (4/146)	0.7% (1/146)	7.7% (4/52)	1.9% (1/52)		
Antoneli et al ²⁷	1986–2003	0.6% (3/470)	0.2% (1/470)	1.1% (2/186)	0.5% (1/186)		
Azar et al ²⁸	1975–2001	1.6% (2/123)	0.0% (0/123)	4.1% (2/49)	0.0% (0/49)		
De Ioris et al ³¹	1999–2012	2.8% (3/107)	0.0% (0/107)	6.7% (3/49)	0.0% (0/49)		
De Potter et al ³²	1972–1992	2.0% (9/440)	0.7% (3/440)	4.0% (8/202)	1.5% (3/202)		
Duncan et al ³³	1990–1998	0.9% (2/226)	0.0% (0/226)			2.4% (2/85) ^a	0.0% (0/85) ^a
Helveston et al ³⁴	1967–1987	1.4% (1/74)	0.0% (0/74)	3.3% (1/30)	0.0% (0/30)		
Jubran et al ³⁵	1991–1999	1.4% (3/207)	0.0% (0/207)				
Jurkiewicz et al ³⁶	1996–2008	0.5% (1/202)	1.0% (2/202)				
Kingston et al ³⁷	1954–1983	1.3% (8/630)	0.5% (3/630)	1.9% (8/432)	0.5% (2/432)		
Lim et al ³⁸	2001–2009	1.4% (2/141)	0.0% (0/141)				
Lim et al ³⁹	1997–2010	3.9% (2/51)	0.0% (0/51)	12.5% (2/16)	0.0% (0/16)		
Lueder et al ⁴⁰	1924–1985	2.3% (3/132)	0.0% (0/132)	6.8% (3/44)	0.0% (0/44)	6.0% (3/50)	0.0% (0/50)
Lueder et al ⁴¹	1924–1989	2.7% (4/143)				7.1% (4/56)	
Moll et al ⁶	1970–1997					5.8% (7/121)	0.0% (0/121)
Moreno et al ³⁰	2000–2009	0.7% (3/438)	0.0% (0/438)	2.2% (3/139)	0.0% (0/139)		
Popovic et al ²⁵	1990–2001	1.8% (4/221)	0.5% (1/221)	3.7% (4/108)	0.9% (1/108)		
Provenzale et al ⁴²	1985–2002	11.1% (7/63)	1.6% (1/63)	23.3% (7/30)	3.3% (1/30)		
Ramasubramanian et al ^{8,21}	2000–2012	1.0% (4/408)		1.6% (3/193)		1.9% (4/215)	
Scott et al ⁴³	1970–1990	5.4% (3/56)	0.0% (0/56)	11.1% (3/27)	0.0% (0/27)	10.0% (3/30)	0.0% (0/30)
Shields et al ²⁰	1995–1999	0.5% (1/214)	0.0% (0/214)	0.9% (1/112)	0.0% (0/112)	0.9% (1/117)	0.0% (0/117)

The number of trilateral retinoblastoma patients divided by the size of the retinoblastoma cohort in parentheses.

^aDuncan et al³³ reported that 83 had hereditary retinoblastoma, excluding the 2 pineal trilateral retinoblastoma cases that can be classified as having hereditary retinoblastoma on the basis of developing a midline primitive neuroectodermal tumor (they also presented a case with an “orbital midline primitive neuroectodermal tumor,” but we are not convinced this is trilateral retinoblastoma).

(6/97) chance to develop trilateral retinoblastoma (5 pineal and 1 suprasellar); excluding the suprasellar tumor from the calculation resulted in a pineal trilateral retinoblastoma incidence of 5.2% (5/97).²² Finally, in a single-center study with 5 cases a pineal trilateral retinoblastoma incidence of 5.7% (5/87) in patients with irradiated hereditary retinoblastoma was reported.²³

• **RISK OF BIAS AND STUDY QUALITY ASSESSMENT:** Per-study scores on individual items of the risk-of-bias checklist (numbered from Q1 through Q6) can be found in [Supplemental Table 2](#) (available at [AJO.com](#)), showing considerable risk of bias in terms of how much the cohort is population-like (Q1 and Q2) and the follow-up duration (Q4). To address assessment bias we compared trilateral retinoblastoma incidence in developed vs developing countries—the latter being potentially more prone to this type of bias, which would result in lower expected incidence numbers. This comparison indeed showed differences with unadjusted unilateral and bilateral trilateral retinoblastoma incidences of 2.3% (95% CI 1.6%–3.2%) vs 1.1% (95% CI 0.5%–1.9%; $P = .32$) and bilateral trilateral retinoblastoma incidences of 6.0% (95% CI 3.5%–9.2%) vs 2.6% (95% CI 0.4%–6.2%; $P = .50$) for developed

and developing countries, respectively, though statistically not significantly different.

DISCUSSION

THIS SYSTEMATIC REVIEW GIVES AN OVERVIEW OF STUDIES on trilateral retinoblastoma incidence. Our summary estimates (especially the adjusted ones) of trilateral retinoblastoma incidence in bilateral or hereditary retinoblastoma are considerably lower than previously summarized by Kivelä,² with an estimated incidence ranging from 5% to 15% in bilateral retinoblastoma, reflecting small cohorts in earlier studies. Even the unadjusted trilateral retinoblastoma incidence from this meta-analysis is lower and more precise (relatively narrow confidence intervals) than generally assumed in “literature”; to test this we evaluated the trilateral retinoblastoma incidence mentioned in the introduction and discussion of articles included in the meta-analysis on survival after trilateral retinoblastoma³ (for obvious reasons, we excluded articles that assessed trilateral retinoblastoma incidence) ([Supplemental Table 3](#), available at [AJO.com](#)).

TABLE 3. The Incidence of Trilateral Retinoblastoma Among Unilateral and Bilateral Retinoblastoma, Bilateral Retinoblastoma, and Hereditary Retinoblastoma for Studies That Assessed the Effect of Previous Chemotherapy or Radiotherapy on the Development of Trilateral Retinoblastoma

Study	Inclusion Period	Treatment for Retinoblastoma	Unilateral and Bilateral Retinoblastoma		Bilateral Retinoblastoma		Hereditary Retinoblastoma	
			Pineal	Nonpineal	Pineal	Nonpineal	Pineal	Nonpineal
Bartuma et al ²⁹	2001–2011	Systemic chemotherapy					0.0% (0/24) ^a	0.0% (0/24) ^a
Chantada et al ¹⁰	1988–2009	Systemic chemotherapy			1.9% (3/159)	0.0% (0/159)		
		No systemic chemotherapy			0.0% (0/38)	0.0% (0/38)		
Klufas et al ²⁴	2006–2010	Intraarterial chemotherapy	1.1% (1/89)	0.0% (0/89)	1.4% (1/70)	0.0% (0/70)		
Ramasubramania et al ^{8,21}	2000–2012	Systemic chemotherapy	0.4% (1/252)				0.6% (1/180)	
		No systemic chemotherapy	1.9% (3/156)				8.6% (3/35)	
Shields et al ²⁰	1995–1999	Systemic chemotherapy	0.0% (0/142)	0.0% (0/142)	0.0% (0/95)	0.0% (0/95)	0.0% (0/99)	0.0% (0/99)
		No systemic chemotherapy	1.4% (1/72)	0.0% (0/72)	5.9% (1/17)	0.0% (0/17)	5.6% (1/18)	0.0% (0/18)
Blach et al ²²	1979–1990	Radiotherapy	4.3% (5/117)	0.9% (1/117)	5.2% (5/97)	1.0% (1/97)		
Imhof et al ²³	1971–1993	Radiotherapy	4.7% (5/106)	0.0% (0/106)			5.7% (5/87)	0.0% (0/87)
Ramasubramanian et al ^{8,21}	2000–2012	Radiotherapy					2.8% (1/87)	
		No radiotherapy					1.7% (3/179)	

The number of trilateral retinoblastoma patients divided by the size of the retinoblastoma cohort in parentheses.

^aTwenty-four patients received a full course of systemic chemotherapy, 1 was previously treated elsewhere, and 2 did not receive (a full course of) chemotherapy; 1 of these latter 2 patients did develop trilateral retinoblastoma (location unspecified).

The lower estimates for trilateral retinoblastoma incidence we calculated potentially reduce the cost-effectiveness of screening for trilateral retinoblastoma in patients with retinoblastoma beyond baseline imaging. More than 50% of trilateral retinoblastomas are diagnosed at the time of retinoblastoma diagnosis (with baseline magnetic resonance imaging of the eyes and brain), suggesting that baseline screening for trilateral retinoblastoma might indeed be useful.³

The few studies that published on prior use of systemic chemotherapy and risk of developing trilateral retinoblastoma have shown conflicting results with respect to a potential decrease of trilateral retinoblastoma risk in patients with retinoblastoma. Whether intraarterial chemotherapy has an effect on the risk to develop trilateral retinoblastoma—theoretically improbable because systemic exposure to chemotherapy is very low—was only assessed in 1 relatively small cohort of 89 patients and does not allow for any conclusions on this issue.²⁴ Also, the few studies that looked at prior radiotherapy did not allow for any meaningful meta-analysis. Should previous radiotherapy (commonly used before the year 1995) be inductive and previous chemotherapy (increasingly used since the year 1995) protective, then we would

expect to see a clear reduction of trilateral retinoblastoma incidence over time. The estimated incidences did slightly decrease after the year 1995, but the differences were not statistically significant (Figure 3). Alternatively, larger cohort sizes in later studies could partially explain this difference.

There is much heterogeneity between the studies reporting trilateral retinoblastoma incidence. Some studies looked at incidence data in a population (3 cohorts from 3 studies; see Table 1), but most are data from 1 or more (specialized) institutions, which—owing to referral bias—might have resulted in a higher trilateral retinoblastoma incidence, or maybe actually a lower incidence when children with trilateral retinoblastoma end up in different specialized pediatric neurooncology centers (Table 2). Also, some of the cohorts are from the same center. Other potential sources of heterogeneity are the choice of start date and end date (year) of the retinoblastoma cohort at risk, and loss to follow-up of patients in the cohort. The estimates in this study assume that of all patients with retinoblastoma in the cohort it is known whether they developed trilateral retinoblastoma, which might be considered appropriate because trilateral retinoblastoma develops relatively quickly (median interval 17 months) after

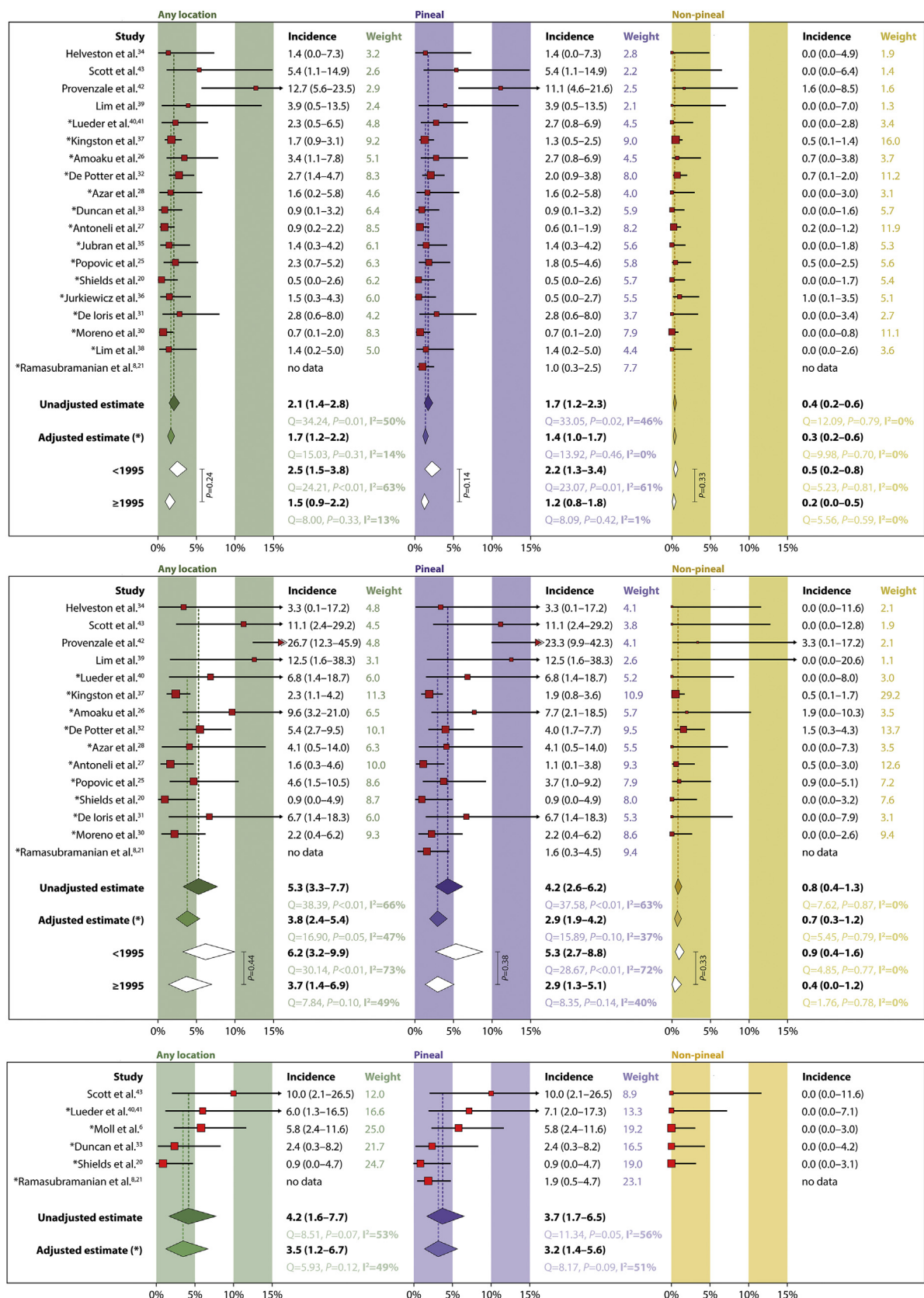


FIGURE 3. Forest plots of trilateral retinoblastoma incidence in cohorts of patients with (Top) unilateral and bilateral, (Middle) bilateral, and (Bottom) hereditary retinoblastoma. Incidence in percentages with a 95% confidence interval in parentheses.

retinoblastoma (since 1995 >95% are diagnosed with trilateral retinoblastoma before the age of 5 years).³

There is a risk that patients with asymptomatic trilateral retinoblastoma without histopathologic proof of disease might have been false-positive trilateral retinoblastoma cases (eg, benign pineal cysts²⁵), causing an overestimation of trilateral retinoblastoma incidence. On the other hand, patients with retinoblastoma, especially those from several

decades back, might have died from central nervous system metastases that were not recognized as trilateral retinoblastoma (ie, false negatives).

In summary the incidence of trilateral retinoblastoma is estimated to be substantially lower than previously reported in the literature concerning trilateral retinoblastoma, especially after adjusting for bias from small cohorts.

FUNDING/SUPPORT: M.C.D.J. WAS SUPPORTED BY THE ODAS FOUNDATION, DELFT, THE NETHERLANDS. THE AUTHOR'S WORK was independent of the funding organization. The funding organization had no involvement in the design or conduct of this study, data management and analysis, or manuscript preparation and review or authorization for submission. Financial disclosures: The following authors have no financial disclosures: Marcus C. De Jong, Wijnanda A. Kors, Pim De Graaf, Jonas A. Castelijns, Annette C. Moll, and Tero Kivela. All authors attest that they meet the current ICMJE criteria for authorship.

REFERENCES

- Jakobiec FA, Tso MO, Zimmerman LE, Danis P. Retinoblastoma and intracranial malignancy. *Cancer* 1977;39(5):2048–2058.
- Kivelä T. Trilateral retinoblastoma: a meta-analysis of hereditary retinoblastoma associated with primary ectopic intracranial retinoblastoma. *J Clin Oncol* 1999;17(6):1829–1837.
- De Jong MC, Kors WA, de Graaf P, Castelijns JA, Kivelä T, Moll AC. Trilateral retinoblastoma: a systematic review and meta-analysis. *Lancet Oncol* 2014;15(10):1157–1167.
- Katayama Y, Tsubokawa T, Yamamoto T, Nemoto N. Ectopic retinoblastoma within the 3rd ventricle: case report. *Neurosurgery* 1991;28(1):158–161.
- Dudgeon J, Lee WR. The trilateral retinoblastoma syndrome. *Trans Ophthalmol Soc U K* 1983;103(5):523–529.
- Moll AC, Imhof SM, Schouten-Van Meeteren AY, Kuik DJ, Hofman P, Boers M. Second primary tumors in hereditary retinoblastoma: a register-based study, 1945–1997. *Ophthalmology* 2001;108(6):1109–1114.
- Moll AC, Imhof SM, Schouten-van Meeteren AYN, Boers M, van Leeuwen F, Hofman P. Chemoreduction for retinoblastoma. *Arch Ophthalmol* 2003;121(10):1513.
- Ramasubramanian A, Kytasty C, Meadows AT, Shields JA, Leahey A, Shields CL. Incidence of pineal gland cyst and pineoblastoma in children with retinoblastoma during the chemoreduction era. *Am J Ophthalmol* 2013;156(4):825–829.e2.
- Marees T, Moll AC, Imhof SM, de Boer MR, Ringens PJ, van Leeuwen FE. Re: more about second cancers after retinoblastoma. *J Natl Cancer Inst* 2010;102(11):831–832.
- Chantada GL, Fandiño AC, Schvartzman E, Raslawski E, Schaiquevich P, Manzitti J. Impact of chemoreduction for conservative therapy for retinoblastoma in Argentina. *Pediatr Blood Cancer* 2014;61(5):821–826.
- Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
- Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
- Murphree AL, Villablanca JG, Deegan WF, et al. Chemotherapy plus local treatment in the management of intraocular retinoblastoma. *Arch Ophthalmol* 1996;114(11):1348–1356.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7(3):177–188.
- Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *J Epidemiol Community Health* 2013;67(11):974–978.
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557–560.
- Hoy D, Brooks P, Woolf A, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012;65(9):934–939.
- Marees T, Moll AC, Imhof SM, de Boer MR, Ringens PJ, van Leeuwen FE. Risk of second malignancies in survivors of retinoblastoma: more than 40 years of follow-up. *J Natl Cancer Inst* 2008;100(24):1771–1779.
- Marees T, van Leeuwen FE, de Boer MR, Imhof SM, Ringens PJ, Moll AC. Cancer mortality in long-term survivors of retinoblastoma. *Eur J Cancer* 2009;45(18):3245–3253.
- Shields CL, Meadows AT, Shields JA, Carvalho C, Smith AF. Chemoreduction for retinoblastoma may prevent intracranial neuroblastic malignancy (trilateral retinoblastoma). *Arch Ophthalmol* 2001;119(9):1269–1272.
- Ramasubramanian A, Meadows AT, Shields JA, Leahey A, Shields CL. Reply to: incidence of pineal gland cyst and pineoblastoma in children with retinoblastoma during the chemoreduction era. *Am J Ophthalmol* 2013;156(6):1320–1321.
- Blach LE, McCormick B, Abramson DH, Ellsworth RM. Trilateral retinoblastoma—incidence and outcome: a decade of experience. *Int J Radiat Oncol Biol Phys* 1994;29(4):729–733.
- Imhof SM, Moll AC, Hofman P, Mourits MP, Schipper J, Tan KE. Second primary tumours in hereditary- and nonhereditary retinoblastoma patients treated with megavoltage external beam irradiation. *Doc Ophthalmol* 1997;93(4):337–344.
- Klufas MA, Gobin YP, Marr B, Brodie SE, Dunkel IJ, Abramson DH. Intra-arterial chemotherapy as a treatment for intraocular retinoblastoma: alternatives to direct ophthalmic artery catheterization. *AJNR Am J Neuroradiol* 2012;33(8):1608–1614.
- Popovic MB, Balmer A, Maeder P, Braganca T, Munier FL, Beck Popovic M. Benign pineal cysts in children with

- bilateral retinoblastoma: a new variant of trilateral retinoblastoma? *Pediatr Blood Cancer* 2006;46(7):755–761.
26. Amoaku WM, Willshaw HE, Parkes SE, Shah KJ, Mann JR. Trilateral retinoblastoma. A report of five patients. *Cancer* 1996;78(4):858–863.
 27. Antoneli CBG, Ribeiro KB, Sakamoto LH, Chojniak MM, Novaes PERS, Arias VEA. Trilateral retinoblastoma. *Pediatr Blood Cancer* 2007;48(3):306–310.
 28. Azar D, Donaldson C, Dalla-Pozza L. Questioning the need for routine bone marrow aspiration and lumbar puncture in patients with retinoblastoma. *Clin Experiment Ophthalmol* 2003;31(1):57–60.
 29. Bartuma K, Pal N, Kosek S, Holm S, All-Ericsson CA. 10-year experience of outcome in chemotherapy-treated hereditary retinoblastoma. *Acta Ophthalmol* 2014;92(5):404–411.
 30. Moreno F, Sinaki B, Fandiño A, Dussel V, Orellana L, Chantada G. A population-based study of retinoblastoma incidence and survival in Argentine children. *Pediatr Blood Cancer* 2014;61(9):1610–1615.
 31. De Ioris MA, Valente P, Randisi F, et al. Baseline central nervous system magnetic resonance imaging in early detection of trilateral retinoblastoma: pitfalls in the diagnosis of pineal gland lesions. *Anticancer Res* 2014;34(12):7449–7454.
 32. De Potter P, Shields CL, Shields JA. Clinical variations of trilateral retinoblastoma: a report of 13 cases. *J Pediatr Ophthalmol Strabismus* 1994;31(1):26–31.
 33. Duncan JL, Scott IU, Murray TG, Gombos DS, van Quill K, O'Brien JM. Routine neuroimaging in retinoblastoma for the detection of intracranial tumors. *Arch Ophthalmol* 2001;119(3):450–452.
 34. Helveston EM, Knuth KR, Ellis FD. Retinoblastoma. *J Pediatr Ophthalmol Strabismus* 1987;24(6):296–300.
 35. Jubran RF, Erdreich-Epstein A, Butturini A, Murphree AL, Villablanca JG. Approaches to treatment for extraocular retinoblastoma: Children's Hospital Los Angeles experience. *J Pediatr Hematol Oncol* 2004;26(1):31–34.
 36. Jurkiewicz E, Pakuła-Kościeszka I, Rutynowska O, Nowak K. Trilateral retinoblastoma: an institutional experience and review of the literature. *Childs Nerv Syst* 2010;26(1):129–132.
 37. Kingston JE, Plowman PN, Hungerford JL. Ectopic intracranial retinoblastoma in childhood. *Br J Ophthalmol* 1985;69(10):742–748.
 38. Lim YS, Juraida E, Alagaratnam J, Menon BS. Trilateral retinoblastoma. *Med J Malaysia* 2011;66(2):156–157.
 39. Lim FPM, Soh SY, Iyer JV, Tan AM, Swati H, Quah BL. Clinical profile, management, and outcome of retinoblastoma in Singapore. *J Pediatr Ophthalmol Strabismus* 2013;50(2):106–112.
 40. Lueder GT, Judisch F, O'Gorman TW. Second nonocular tumors in survivors of heritable retinoblastoma. *Arch Ophthalmol* 1986;104(3):372–373.
 41. Lueder GT, Judisch GF, Wen BC. Heritable retinoblastoma and pinealoma. *Arch Ophthalmol* 1991;109(12):1707–1709.
 42. Provenzale JM, Gururangan S, Klintworth G. Trilateral retinoblastoma: clinical and radiologic progression. *AJR Am J Roentgenol* 2004;183(2):505–511.
 43. Scott MH, Richard JM. Retinoblastoma in the state of Oklahoma: a clinicopathologic review. *J Okla State Med Assoc* 1993;86(3):111–118.



Biosketch

Marcus C. de Jong, MD, MSc, is a resident and PhD student at the department of Radiology and Nuclear Medicine at the VU University Medical Center, Amsterdam (the Netherlands). With a background in medicine and clinical epidemiology (he received both degrees from the Erasmus University Rotterdam) he has been working on various topics in the field of retinoblastoma (with a focus on the use of magnetic resonance imaging, but also on epidemiological topics) since 2012.

SUPPLEMENTAL TABLE 1. The Syntaxes Used to Obtain Articles That Reported Incidence of Trilateral Retinoblastoma With Pubmed and Embase

Pubmed search syntax^a:

("Retinoblastoma"[Mesh] OR retinoblastoma[tw] OR retinoma[tw] OR retinocytoma[tw]) AND ("Pinealoma"[Mesh] OR pinealoma[tw] OR pineoblastoma[tw] OR pinealoblastoma[tw] OR pineal[tw] OR trilateral[tw] OR ectopic[tw] OR brain[tw] OR sellar[tw] OR suprasellar[tw] OR parasellar[tw]) AND (("1966/01/01"[PDAT] : "3000/12/31"[PDAT]) AND (Dutch[lang] OR English[lang] OR German[lang])) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])

The Embase search syntax^a:

('retinoblastoma' OR 'retinoblastoma'/exp OR retinoblastoma OR 'retinoma' OR 'retinoma'/exp OR retinoma OR 'retinocytoma' OR 'retinocytoma'/exp OR retinocytoma) AND ('pinealoma' OR 'pinealoma'/exp OR pinealoma OR pineoblastoma OR 'pinealoblastoma' OR 'pinealoblastoma'/exp OR pinealoblastoma OR pineal OR trilateral OR ectopic OR 'brain' OR 'brain'/exp OR brain OR sellar OR suprasellar OR parasellar) AND [humans]/lim AND [embase]/lim AND ([dutch]/lim OR [english]/lim OR [german]/lim) AND [medline]/lim AND [1966–2015]/py

^aBoth searches were performed on March 14, 2014 and updated on July 15, 2015.

SUPPLEMENTAL TABLE 2. Risk-of-Bias Assessment With a Modified Checklist by Hoy and Associates¹⁷ of the Studies That Assessed the Incidence of Trilateral Retinoblastoma and Were Included in This Systematic Review and Meta-analysis

Author	Q1	Q2	Q3	Q4	Q5	Q6
Amoaku et al ²⁶	1	2	2	0	2	1
Antoneli et al ²⁷	2	0	2	2	2	1
Azar et al ²⁸	2	0	2	0	0	0
Bartuma et al ²⁹	0	0	0	1	2	0
Blach et al ²²	0	0	0	2	2	1
Chantada et al ¹⁰		0	2	2	0	1
De Ioris et al ³¹	2	0	2	0	2	1
De Potter et al ³²	0	0	2	0	2	1
Duncan et al ³³	1	0	2	1	2	1
Helveston et al ³⁴	2	0	2	0	2	1
Imhof et al ²³	0	0	2	2	2	1
Jubran et al ³⁵	0	0	2	0	2	1
Jurkiewicz et al ³⁶	0	0	2	0	0	1
Kingston et al ³⁷	0	0	2	0	2	1
Klufas et al ²⁴	0	0	0	0	2	0
Lim et al ³⁸	0	0	2	0	2	1
Lim et al ³⁹	0	0	2	1	2	1
Lueder et al ⁴⁰	0	0	2	0	2	1
Lueder et al ⁴¹	0	0	2	0	2	1
Moll et al ⁶		2	2	2	2	1
Moreno et al ³⁰	0	2	2	0	2	1
Popovic et al ²⁵	0	0	0	0	2	1
Provenzale et al ⁴²	0	0	2	0	2	1
Ramasubramanian et al ^{8,21}	0	0	0	0	2	1
Scott et al ⁴³	0	0	2	0	2	1
Shields et al ²⁰	0	0	2	0	2	0

0 = high risk, 1 = intermediate risk, 2 = low risk.

Q1. Was the study's target population a close representation of the national population in relation to relevant variables? (Based on Marees et al.,^{18,19} ie, 39.4% bilateral cases)

0 points: proportion of bilateral deviates considerably (≥ 6 percentage points [%pts]) from population-like or undefined.

1 point: proportion of bilateral deviates slightly (3–6 %pts) from population-like.

2 points: proportion of bilateral population-like (< 3 %pts).

Q2. Was the sampling frame a true or close representation of the target population? (eg, hospital-based: high risk, population-based: low risk)?

0 points: hospital-based or undefined.

2 point: national or regional population.

Q3. Was some form of random selection used to select the sample, OR was a census undertaken?

0 points: selected cases (eg, based on type of therapy or undefined).

2 points: consecutive cases.

Q4. Was the likelihood of patients missing from follow-up minimal? Was the length of the shortest prevalence period for the parameter of interest appropriate? (ie, adequate length of follow-up to observe the outcome)

0 points: median follow-up < 2.5 years or undefined.

1 point: median follow-up ≥ 2.5 but < 5 years.

2 points: median follow-up ≥ 5 years.

Q5. Was an acceptable case definition used in the study?

0 points: temporal clustering of cases with increasing follow-up or unclear.

2 points: no evidence of temporal clustering of cases with increasing time period.

Q6. Was the way of trilateral retinoblastoma assessment appropriate (eg, histopathology, cerebrospinal fluid and on imaging: treatment response to therapy or disease progression)?

0 points: undefined.

1 point: clinical diagnosis including imaging.

2 points: based on histopathology.

SUPPLEMENTAL TABLE 3. Trilateral Retinoblastoma Incidence Mentioned in the Introduction or Discussion of Articles Since 2000 Included in our Meta-analysis on Trilateral Retinoblastoma Survival,¹ Excluding Articles That Assessed Trilateral Retinoblastoma Incidence

Study	Year	Retinoblastoma Population	Incidence of Trilateral Retinoblastoma	Source According to Authors
Bonci et al ²	2013	Bilateral	8%–10%	Kivelä ³
Dai et al ⁴	2008	Unilateral or bilateral	3%	Bader et al, ⁵ Amoaku et al, ⁶ De Potter et al, ⁷ Pesin et al ⁸
Dimaras et al ⁹	2011	Unilateral or bilateral	3%	De Potter et al ⁷
D'Elia et al ¹⁰	2014	Sporadic unilateral	<0.5%	De Potter et al ⁷
		Sporadic bilateral	5%–13%	
		Familial bilateral	5%–15%	
Dunkel et al ¹¹	2010	Bilateral	6%	Blach et al ¹²
Huddleston et al ¹³	2013	Genetic form	3%–9%	Blach et al, ¹² Shields et al ¹⁴
Ibarra et al ¹⁵	2000	Unilateral	0.5%	Kingston et al, ¹⁶ De Potter et al, ⁷ Blach et al ¹²
		Bilateral	4%–10%	
James et al ¹⁷	2010	Unilateral or bilateral	1.5%–5%	Provenzale et al ¹⁸
Kamaleshwaran et al ¹⁹	2014	Sporadic unilateral	<0.5%	Kivelä ³
		Sporadic bilateral	5%–13%	
		Familial bilateral	5%–15%	
Kivela et al ²⁰	2003	Hereditary	5%–15%	Kivelä, ³ Kingston et al, ¹⁶ Blach et al, ¹² De Potter et al ⁷
Raizis et al ²¹	2013	Unspecified	<1%	Antoneli et al ²²
Rodjan et al ²³	2012	Sporadic unilateral	<0.5%	De Potter et al, ⁷ Kivelä ³
		Sporadic bilateral	5%–13%	
		Familial bilateral	5%–15%	
Popovic et al ²⁴	2006	Unspecified	4%–8%	Kingston et al, ¹⁶ De Potter et al, ⁷ Shields et al ²⁵
Popovic et al ²⁶	2007	Sporadic unilateral	<0.5%	Kivelä ³
		Sporadic bilateral	5%–13%	
		Familial bilateral	5%–15%	
Shah et al ²⁷	2013	All	3%	Shields et al ²⁶
		Unilateral	0.5%	
		Bilateral	2%–11%	
Skrypnyk et al ²⁹	2004	Unspecified	5%	De Potter et al ⁷
Tsuruta et al ³⁰	2011	All	3%	De Potter et al ⁷
Wright et al ³¹	2010	Genetic form	3%–9%	Blach et al ¹²

References for Supplemental Table 3.

- De Jong MC, Kors WA, de Graaf P, Castelijns JA, Kivelä T, Moll AC. Trilateral retinoblastoma: a systematic review and meta-analysis. *Lancet Oncol* 2014;15(10):1157–1167.
- Bonci GA, Rosenblum MK, Gilheeneey SW, Dunkel IJ, Holodny AI. Diffusion-weighted imaging to assess treatment response in a child with trilateral retinoblastoma. *Pediatr Radiol* 2013;43(9):1231–1234.
- Kivelä T. Trilateral retinoblastoma: a meta-analysis of hereditary retinoblastoma associated with primary ectopic intracranial retinoblastoma. *J Clin Oncol* 1999;17(6):1829–1837.
- Dai S, Dimaras H, Héon E, et al. Trilateral retinoblastoma with pituitary-hypothalamic dysfunction. *Ophthalmic Genet* 2008;29(3):120–125.
- Bader JL, Miller RW, Meadows AT, Zimmerman LE, Champion LA, Voûte PA. Trilateral retinoblastoma. *Lancet* 1980;2(8194):582–583.
- Amoaku WM, Willshaw HE, Parkes SE, Shah KJ, Mann JR. Trilateral retinoblastoma. A report of five patients. *Cancer* 1996;78(4):858–863.
- De Potter P, Shields CL, Shields JA. Clinical variations of trilateral retinoblastoma: a report of 13 cases. *J Pediatr Ophthalmol Strabismus* 1994;31(1):26–31.
- Pesin SR, Shields JA. Seven cases of trilateral retinoblastoma. *Am J Ophthalmol* 1989;107(2):121–126.
- Dimaras H, Héon E, Doyle J, et al. Multifaceted chemotherapy for trilateral retinoblastoma. *Arch Ophthalmol* 2011;129(3):362–365.
- D'Elia G, Grotta S, Del Bufalo F, et al. Two novel cases of trilateral retinoblastoma: genetics and review of the literature. *Cancer Genet* 2013;206:398–401.
- Dunkel IJ, Jubran RF, Gururangan S, et al. Trilateral retinoblastoma: potentially curable with intensive chemotherapy. *Pediatr Blood Cancer* 2010;54(3):384–387.
- Blach LE, McCormick B, Abramson DH, Ellsworth RM. Trilateral retinoblastoma—incidence and outcome: a decade of experience. *Int J Radiat Oncol Biol Phys* 1994;29(4):729–733.
- Huddleston S, McNall-Knapp RY, Siatkowski M, Odom C, Brennan R, Wilson MW. A novel translocation t(11;13) (q21;q14.2) in a child with suprasellar primitive neuroectodermal tumor and retinoblastoma. *Ophthalmic Genet* 2013;34(1-2):97–100.
- Shields CL, Mashayekhi A, Cater J, Sheli A, Meadows AT, Shields JA. Chemoreduction for retinoblastoma: analysis of tumor control and risks for recurrence in 457 tumors. *Trans Am Ophthalmol Soc* 2004;102:35–44; discussion 44–45.

15. Ibarra MS, O'Brien JM. Is screening for primitive neuroectodermal tumors in patients with unilateral retinoblastoma necessary? *J AAPOS* 2000;4(1):54–56.
16. Kingston JE, Plowman PN, Hungerford JL. Ectopic intracranial retinoblastoma in childhood. *Br J Ophthalmol* 1985;69(10):742–748.
17. James SH, Halliday WC, Branson HM. Best cases from the AFIP: Trilateral retinoblastoma. *Radiographics* 2010;30(3):833–837.
18. Provenzale JM, Weber AL, Klintworth GK, McLendon RE. Radiologic-pathologic correlation. Bilateral retinoblastoma with coexistent pinealoblastoma (trilateral retinoblastoma). *AJNR Am J Neuroradiol* 1995;16(1):157–165.
19. Kamaleshwaran KK, Shibu DK, Mohanan V, Shinto AS. Rare case of trilateral retinoblastoma with spinal canal drop metastasis detected with fluorine-18 fluorodeoxyglucose positronemission tomography/computed tomography imaging. *Indian J Nucl Med* 2014;29(2):115–116.
20. Kivelä T, Tuppurainen K, Riikonen P, Vapalahti M. Retinoblastoma associated with chromosomal 13q14 deletion mosaicism. *Ophthalmology* 2003;110(10):1983–1988.
21. Raizis AM, Van Mater D, Aaltonen LA, et al. Trilateral retinoblastoma in a patient with Peutz-Jeghers syndrome. *Am J Med Genet A* 2013;161A(5):1096–1100.
22. Antoneli CBG, Ribeiro KB, Sakamoto LH, Chojniak MM, Novaes PERS, Arias VEA. Trilateral retinoblastoma. *Pediatr Blood Cancer* 2007;48(3):306–310.
23. Rodjan F, de Graaf P, Brisse HJ, et al. Trilateral retinoblastoma: neuroimaging characteristics and value of routine brain screening on admission. *J Neurooncol* 2012;109(3):535–544.
24. Popovic MB, Balmer A, Maeder P, Braganca T, Munier FL, Beck Popovic M. Benign pineal cysts in children with bilateral retinoblastoma: a new variant of trilateral retinoblastoma? *Pediatr Blood Cancer* 2006;46(7):755–761.
25. Shields J, Shields C. Genetics of retinoblastoma. In: Shields J, Shields C, editors. *Intraocular Tumors: A Text and Atlas*. Vol Philadelphia: WB Saunders; 1992:333–339.
26. Popovic MB, Diezi M, Kuchler H, et al. Trilateral retinoblastoma with suprasellar tumor and associated pineal cyst. *J Pediatr Hematol Oncol* 2007;29(1):53–56.
27. Shah I, Baig A, Razzaq A, Faruqi A, Ali A, Khan FQ. Trilateral retinoblastoma with unilateral eye involvement. *J Pak Med Assoc* 2013;63(7):910–912.
28. Shields CL, Meadows AT, Shields JA, Carvalho C, Smith AF. Chemoreduction for retinoblastoma may prevent intracranial neuroblastic malignancy (trilateral retinoblastoma). *Arch Ophthalmol* 2001;119(9):1269–1272.
29. Skrypnik C, Bartsch O. Retinoblastoma, pinealoma, and mild overgrowth in a boy with a deletion of RB1 and neighbor genes on chromosome 13q14. *Am J Med Genet A* 2004;124A(4):397–401.
30. Tsuruta T, Aihara Y, Kanno H, et al. High-dose chemotherapy followed by autologous and allogeneic peripheral blood stem cell transplantation for recurrent disseminated trilateral retinoblastoma. *Childs Nerv Syst* 2011;27(6):1019–1024.
31. Wright KD, Qaddoumi I, Patay Z, Gajjar A, Wilson MW, Rodriguez-Galindo C. Successful treatment of early detected trilateral retinoblastoma using standard infant brain tumor therapy. *Pediatr Blood Cancer* 2010;55(3):570–572.